REVIEW ARTICLE

Pancreatic Cancer – Low Survival Rates

Hans G. Beger, Bettina Rau, Frank Gansauge, Gerd Leder, Michael Schwarz, Bertram Poch

SUMMARY

Introduction: Cancers of the pancreas are identified in 11 800 to 13 500 patients each year in Germany. Epidemiological studies prove smoking and chronic alcohol consumption as causes of about 30% of pancreatic cancers.

Methods: Selective literature review.

Results: Only patients within TNM stage I and II have after oncologic tumor extirpation a chance for long term survival. Controlled prospective clinical trials demonstrated adjuvant chemotherapy yielding an additional significant survival benefit. The 3- and 5-year-survival after R0-resection and adjuvant chemotherapy are about 30% and below 15% respectively. Using the criteria of observed 5-year-survival less than 2% of all pancreatic cancer patients are alive. After R0-resection the median survival time is between 17 and 28 months, after R1/2-resection between 8 and 22 months.

Discussion: Pancreatic cancer is even today for more than 95% of the patients incurable. Strategies to prevent pancreatic cancer are intended to stop smoking and chronic alcohol consumption and early surgical extirpation of cystic neoplastic lesions. For patients with established pancreatic cancer risk a follow-up protocol is discussed.

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Key words: pancreatic cancer, systemic disease, early cancer dissemination into nerves, lymph tissue and blood circulation, R0-resection, adjuvant chemotherapy

Abteilung für Allgemein- und Viszeralchirurgie, Klinikum der Universität Ulm (1982 bis 2001): Prof. em. Dr. med. Dr. h. c. Beger, PD Dr. med Rau, PD Dr. med. Gansauge, PD Dr. med. Schwarz, PD Dr. med. Poch

Zentrum für Onkologische, Endokrinologische und Minimalinvasive Chirurgie Neu-Ulm: Prof. em. Dr. med. Dr. h. c. Beger, PD Dr. med. Gansauge, PD Dr. med. Schwarz, PD Dr. med. Poch

Abteilung für Allgemeine, Thorax-, Gefäß- und Transplantationschirurgie, Universität Rostock: PD Dr. med. Rau

Abteilung für Allgemein-, Visceralchirurgie und Transplantationschirurgie, Klinikum der Universität Ulm: Dr. med. Leder

Cancers of the pancreas are identified in 11 800 to 13 500 patients each year in Germany (1). The mean age at disease onset is 68 years in men and 70 years in women. For some years, women have been observed to develop the disease more frequently than men (1). The growing incidence of pancreatic cancer in the industrialized countries is attributed to overweight (2), increasing age, smoking (4), and chronic alcohol consumption (4). Epidemiological studies have shown smoking to be the cause in about 30% of cases of ductal pancreatic cancer (3); pancreatic diseases with a markedly elevated risk of malignancy – besides the genetically determined syndromes with high pancreatic carcinoma penetrance (5) – are hereditary chronic pancreatitis with up to 40% malignancy (6), chronic alcoholic pancreatitis with 4% to 6 % malignancy (7), and cystic neoplasms with a malignant transformation rate of 20% to 70% (8).

Pancreatic cancer is still incurable for more than 95% of patients (9). In preparation for exercising the function of expert (Beger), and as a member of the Surgical Treatment Working Group for drafting of the S3 guidelines of the German Society of Digestive and Metabolic Diseases (DGVS)/ of the Scientific Medical Societies in Germany (AWMF) (Rau), the authors conducted a selective literature review based on their clinical and scientific experience.

A systemic disease?

The prognosis of ductal pancreatic cancer is determined by very early lymphogenic (10), neurogenic (11), and hematogenic dissemination of cancer cells *(table 1)*. In >90% of patients, the cancer has spread beyond the anatomic boundaries of the pancreas at the time of diagnosis (e1–e7); about one third of these patients are diagnosed in the metastatic stage. The TNM classification 2002 takes into account tumor size, carcinomatous involvement of the peripancreatic lymph nodes, and metastatic pattern as prognostic factors (12) *(table 2)*. Following radical surgical removal of the tumor, tumor biological factors have a significantly positive influence on survival if the tumor measures less than 2 cm, if there is no lymph node metastasis and no infiltration into extrapancreatic nerves and nerve plexus and the vessel walls are not infiltrated (e8–e14) *(table 3)*. When molecular biological or immunohistological methods are used to detect

TABLE 1

Dissemination pathways of ductal pancreatic cancer

Lymphogenic	Lymph nodes Lymph vessels: carcinomatous lymphangiosis	T1 64%, T4 > 90% (e1) 67% (8, e2)
Perineural	Intrapancreatic nerves Perivascular nerves Extrapancreatic nerve plexus	90% (e3) 38% AMS (e4) see table 4
Hematogenic	Liver Bone marrow	36% to 65% (e5) 24% to 59% (e6)
Intraperitoneal	Free, vital cancer cells in peritoneal cavity	8% to 33% (e7)
Local	Common bile duct Duodenum Portal vein, mesenteric vein, HA, SMA Small intestinal mesenterium Mesenterium of transverse colon Peritoneum	

HA, hepatic artery; SMA, superior mesenteric artery;
The data cited represent a selection of the results published for the respective tissue from large prospective studies.

TABLE 2

TNM classification of pancreatic cancer

UICC stage	Tumor extent	Lymph node involvement*	Macro-metastases	Residual tumor
0	Tis in situ	N0	M0	R0
IA	T1 < 2 cm			
B	T2 > 2 cm	N0	M0	
IIA	T3 > pancreas	N0	M0	R1
B	T1–3	N (regional)	M0	R2
III	T4 in CA/SMA	N0 – 1	M0	
IV	T1–4	N0 – 1	M+	

CA, celiac artery; SMA, superior mesenteric artery;
*pN0 (i+) histologically N0, immunomorphologically isolated TM cells positive,
pN0 (mol+) histologically N0, RT-PCR isolated tumor cells positive;
UICC, Union International Contre le Cancer / International Union against Cancer;
R0 = resection margins histologically cancer cell free;
R1 = resection margins histologically cancer cell positive;
R2 = residual tumor macroscopically positive:
TNM Classification of Malignant Tumors 2003, Springer, 6th Edition, pp. 86-88 (12).

malignant cells, it has been shown that in many cases ductal pancreatic cancer is a disease that is generalized at an early stage (13, 14). With the polymerase chain reaction (PCR) and immunohistological techniques, disseminated cancer cells can be detected in bone marrow and in the liver in 36% to 76% of cases (13, 14). Lymph nodes that are free from cancer cells on light microscopic examination are found to have cancer cells in about 50% of cases when using molecular biological techniques (e15–e21) *(table 4)*.

Pain

There are no early symptoms associated with the onset of pancreatic cancer. Upper abdominal pain, back pain, sudden onset diabetes, jaundice and fatty stools as well as unexplained weight loss are late symptoms caused by advanced pancreatic cancer.

Characteristic features of advanced pancreatic cancer are pain, often with a right or left sided point of maximum intensity depending on the localization (head or body/tail of pancreas) (e22). Many patients are initially treated by an orthopedist for back pain, often for long periods. Pain associated with the primary tumor and the relapsing cancer is caused by the characteristically pronounced neurotrophic cancer cell dissemination seen in pancreatic cancer (15) *(table 5)*.

A typical feature is the early spread along the intra- and extrapancreatic nerves (e23, e24). Pancreatic cancer cells first infiltrate the perineurium and associate with the Schwann cells and axons in the endoneurium of the intrapancreatic nerves. Histological analysis reveals nerve plexus infiltrations outside the pancreas (superior and inferior mesenteric plexus, celiac plexus, and plexus of the superior mesenteric artery) in 43% to 72% of examined patients (e2, e4, e24–e27). The affinity of the cancer cells to spread along the nerves correlates with the proliferation promoting action of

neurotrophic growth factors. The nerve growth factor and its receptors are elevated in pancreatic cancer cells intra- and extrapancreatically and also stimulate the dissemination of the cancer cells (e28, e29).

Diagnosis

If the clinical data give rise to the suspicion of pancreatic cancer, the present standard diagnostic technique is thinlayer contrast CT (CECT) or multidetector CT (MDCT) or magnetic resonance imaging (MRI) (e30–e33). The sensitivity and specificity is between 82% and 93% for MDCT (16) and between 85% and 95% for MRI (17). The limits of diagnostic accuracy for modern CT and MRI methods are reached at a tumor size of 3 to 5 mm, equivalent to a carcinoma mass of $>10^8$ cells (e34). Endoscopic ultrasound (EUS), when performed by an experienced specialist, offers a similarly high level of diagnostic accuracy, especially for pancreas head cancer (e35). The use of positron emission tomography (PET) for initial diagnosis, while more cost intensive, has not to date provided greater diagnostic reliability. 15% to 35% of patients with diagnosed pancreatic cancer are classified as operable. 10% to 20% of the patients classified as operable, however, are found to have hepatic metastases measuring less than 5 mm or peritoneal metastases that still elude MDCT or MRI detection (18). For patients with TNM stage T3, it may therefore be advisable to perform presurgical laparoscopy to rule out small hepatic and peritoneal metastases and free tumor cells in the ascites (e36). Histological detection of pancreatic cancer by CT or ultrasound guided tumor biopsy is rarely necessary and can cause dissemination of peritoneal malignant cells. Tumor biopsy is justified, however, when after considering the risk factors tumor staging is not possible despite an extended diagnostic program. The risk of disseminating cancer cells is avoided by sonographically guided transduodenal tumor biopsy (e37). The life expectancy of patients in TNM stage I or II can be increased by R0 tumor resection *(table 6)*. A significant survival benefit was also achieved in TNM stage III by surgery in combination with palliative chemotherapy compared to bypass operation with chemotherapy (e38, e39). The advantage of surgical removal of a TNM III cancer compared to other therapeutic principles, however, remains to be demonstrated in further prospective studies. *Figure 1* presents the diagnostic algorithm for suspected pancreatic cancer in conformity with the S3 guidelines (19).

TABLE 3

Tumor biological factors with positive influence on postoperative survival in ductal pancreatic cancer

Tumor size (T)	< 2 to 3 cm	Tsuchia 1985 (e8)
LN metastases	Negative	Cameron 1991 (e9)
Extrapancreatic nerve infiltrates	Negative	Nagakawa 1991 (e10)
Vessel wall infiltration	negative	Ishikawa 1996 (e11)
Degree of cell differentiation	G1	Geer + Brennan 1993 (e12)
DNA content	Diploid	Yeo + Cameron 1997 (e12)
Gene mutations	Wild-type p53, p16, DPC 4, K-ras	Kleef + Büchler 2006 (e14)

Selection of publications published for the respective finding with significance for postoperative survival calculated by the Kaplan-Meier method

Surgical treatment

An indication for oncological resection is present at TNM stage I and II. Tumor removal is achieved in

TABLE 4

Detection of disseminated tumor cells of HE-negative (pN0) lymph nodes*[1]

	No. of patients positive/total	Pancreatic cancer stage	Incidence DTC pos.	Determination method	Lymph node region
ANDO 1997 (e15)	8/15	No data	53%	RT-PCR/K-ras	Paraaortic
HOSCH 1997 (e16)	13/18	II (9pN0)	72%	Immunohistology	N1
Tamagawa 1997 (e17)	12	No data	83%	RT-PCR/K-ras	N1/2
DEMUERE 1998 (e18)	16/22		73%	RT-PCR/K-ras	N1/2
Brown 2001 (e19)	30 30	II/III II/III	63% 47%	Immunohistology RT-PCR/K-ras	N1 N1
Niedergethmann 2002 (e20)	66	No data	17%	RT-PCR/K-ras	N1/2
Kanemitsu 2003 (e21)	7	No data	71%	Immunohistology/ Anti-CK	N2

*DTC, disseminated tumor cells;
HE, hematoxylin-eosin stained sections for microscopic analysis;
K-ras, rasprotein;
RT-PCR, reverse transcription polymerase chain reaction;
Anti-CK, antibody;

*[1] Data of all prospective studies published to date (2006) on the incidence of disseminated tumor cells in pN0 lymph nodes in pancreatic cancer.

TABLE 5

Cancer infiltration into extrapancreatic nerve plexus

Period/studies	No. of patients positive/total	Frequency cancer positive	Nerve plexus	Determination method	Cancer stage
1991–2000*1	165/283	58,3%	PlxMesII/*1 AMS *2	HE RT-PCR/K-ras	T1–T3 (JPS)*3 I–III (JPS)

Summary of data from prospective studies published to date on the incidence of extrapancreatic nerve plexus infiltration
*1 PlxMesII, mesenteric plexus II (right); Kayahara 1991 (e25), Nagakawa 1992 (e26), Takahashi 1992 (e2), Nakao 1996 (e27), Ohigashi 2000 (e4);
*2 SMA, superior mesenteric artery plexus;
*3 JPS, Japan Classification System.

10% to 25% of patients with pancreatic cancer. Radical surgical removal of cancer prolongs life expectancy by one to three years and improves quality of life (20, 24, 25). For patients with a tumor which has spread beyond the pancreas (TNM stage IIB, III) and with clinically suspected metastasis into regional lymph nodes, the surgical removal of carcinoma is frequently palliative in nature; compared to a bypass operation, palliative tumor removal, when possible, can achieve a median survival of 8 to 20 months (e38, e39). For cystic neoplasms of the pancreas – mucinous cystic neoplasm (MCN) and intraductal papillary mucinous cystic neoplasm (IPMN) – radical tumor removal is also indicated for large cancers because median survival and long-term survival are much more favorable than for ductal adenocarcinoma. For invasive cancers that have developed from an IPMN, the 5-year survival rate is between 35% and 45% (8).

Enlarged lymph nodes in the peripancreatic compartment imaged in CT or EUS are frequently, but not invariably, the expression of lymph node metastasis. Enlarged regional lymph nodes (TNM stage N1) are not a contraindication for surgical treatment because these lymph nodes are extirpated in a standardized oncological tumor removal procedure without increasing the surgical risk. The removal of at least 10 lymph nodes is required for postoperative lymph node staging *(figure 2)*.

Pylorus preserving resection of the pancreas head is now the acknowledged standard procedure, and compared to Kausch-Whipple resection offers the advantage of complete preservation of the stomach. With standardized tissue dissection 10 to 25 lymph nodes, and with an extensive dissection technique 20 to 50 lymph nodes are obtained in the specimen.

At high volume centers, hospital mortality is well below 5% (e42–e49) *(table 7)*. Local complications necessitating reintervention or reoperation are ruptured sutures at the pancreatic anastomosis, volume relevant intra-abdominal bleeding necessitating blood transfusion, and abscess formation in the operative field. Reoperation rates at centers with more than 30 pancreas operations per year are 3% to 8% (e50).

TABLE 6

Resection of pancreatic cancer, resection margin infiltration and survival times, results of all large (≥ 75 patients) prospective follow-up studies published to date

	Patients (number)	Resection margin positive (R1/R2) number/%	Median survival Resection margin pos (R1/2) months	Median survival Resection margin neg (R0) months
Yeo 1995 (e50)	201	58 (29%)	10	18
Millikan 1999 (e52)	75	22 (29%)	8	17
Sohn 2000 (e53)	616	184 (30%)	12	19
Benassai 2000 (e54)	75	15 (20%)	9	26
Neoptolemos 2001 (e55)	541	101 (19%)	11	17
Raut 2006 (e56)	No data	60 (16.7%)	22	28

Cancer of the left pancreas

Patients with cancer in the body and tail region are usually diagnosed with a tumor that has passed beyond the boundary of the organ. Frequently there is infiltration into the splenic vein and portal vein wall and direct retropancreatic spread. Every second patient has hepatic metastases at the time of diagnosis. Subtotal resection of the left pancreas, including vascular wall resection and removal of the spleen and if necessary removal of the left adrenal, is possible in only 8% to 15% of patients (e51). Extensive resection can provide a 5-year probability of survival of 22%, and standard resection 8% (22).

In R0 resected patients with pancreatic head/tail cancer, median survival times of 10 to 16 months are achieved (21), (e40, e41). Patients with left pancreatic cancer consecutive to cystic neoplasia (a mucinous cystic adenoma or an IPMN tumor is the commonest underlying condition) should undergo oncological resection whenever possible; R0 resection provides a 5-year probability of survival of 35% to 45% in mucinous cystic cancers (8, e40, e41).

Postresection prognosis

In a curative-intent resection of head of pancreas cancer, cancer cell infiltrates are detected postoper-

atively in the resection margins in one third of patients *(table 6)*. Median survival times after R0 resection are between 17 and 28 months; with R1/R2 resection the median survival is between 8 and 22 months (e50, e52–e56). Kaplan-Meier calculation of the probability of survival after R0 resection shows a 1-, 3-, and 5-year survival of 80%, 35%, and below 20% respectively (20, 23, 25, e8). If long-term follow-up of radically operated patients is used as the basis for estimating the prognosis, however, a cure is documented in less than 2% of resected patients post R0 resection (9, 24). Recurrence of pain due to the cancer infiltrating the nerves, lymph node metastases, and locoregional microscopic tumor cell residues are identifying symptoms of local relapse. This is very common and escapes CT diagnosis if no extensive tumor formation is present. In most cases the cause of death is not the local relapse but the progressive organ metastasis. A considerable number of patients die not from the progressive tumor but from paraneoplastic syndromes.

Limitations of resective therapy

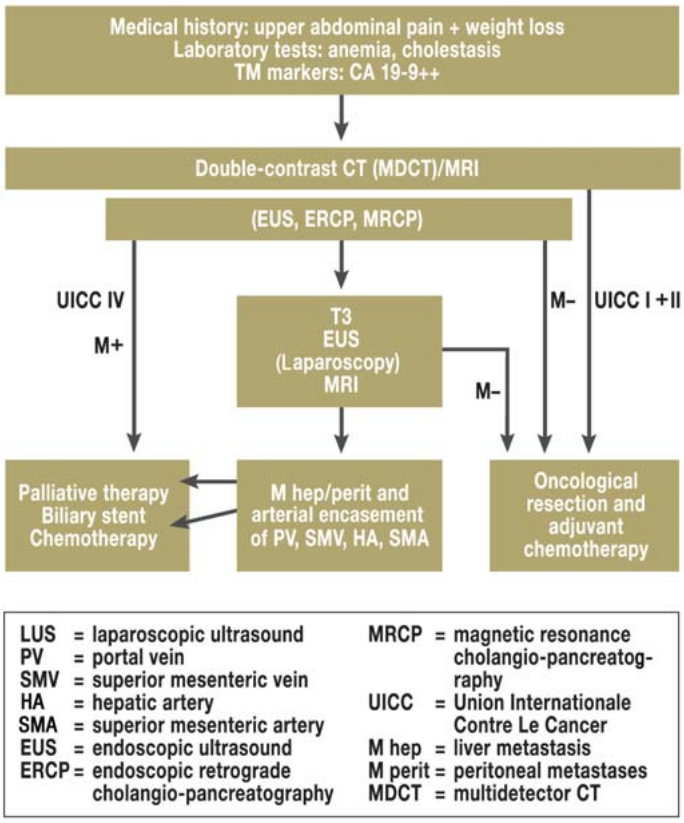
Curative-intent tumor extirpation is reported in large series between 70% and 85% (e50, e52–e56).

Radical surgical tumor removal, i.e. R0 resection of the tumor bearing organ and the neighboring lymph, fat, and nerve compartment, only offers the possibility of a cure for tumors of TNM stages I and II. Patients with a pancreatic tumor measuring less than 2 cm and which has not infiltrated into lymph tissue and nerves outside the pancreas can survive for long periods after successful resection.

In large multicenter studies published in recent years, the 5-year probabilities of cure after surgical tumor removal are below 20% (20, 25). Survival figures calculated by the Kaplan-Meier method are statistical statements regarding the probabilities of a cure, not of actual cure of pancreatic cancer. A review of the published data for observed long-term survival after cancer resection shows that survival after five and more years is dramatically low at 5% for radically resected patients (9, 23). The question regarding the influence of the radicality principle on the probability of cure – local or extensive radical tissue dissection – cannot yet be answered conclusively due to the lack of controlled data. The available results of randomized controlled clinical studies, however, suggest that extensive radical tissue dissection of small tumors (TNM stages I and II) provides improved local tumor control, but no increase in the 5-year probability of cure (e57–e60). Tumor patients operated in tumor stage III had a median survival of 13.7 months *(figure 3)*. After R0 tumor removal, i.e. with resection margins histologically free from tumor cells, there is no certainty of complete radical cancer removal because 15% to 45% have microscopic tumor cell residues (24). About 50% of patients have extrapancreatic nerve and plexus infiltrates *(table 5)*. The local relapse is the consequence of tumor cell nests left in situ.

The course is determined by a local relapse which frequently begins with pain, i.e. a recurrence also in the nerve tissue. After R0 resection, i.e. local complete cancer removal, the course is frequently determined by metastases in the liver

FIGURE 1



Pancreatic cancer, diagnostic algorithm (Surgical Clinic I, Ulm University Hospital)

TABLE 7

Pancreatic cancer, low hospital mortality at high-volume centers, results of large national multicenter comparative studies

	Hospital mortality	
	High-volume centers*1	Low-volume centers
Maryland USA 1995 (e42)	2,2%	19%
New York USA 1995 (e43)	5,5%	18,9%
Netherlands, Dutch 1997 (e44)	1,5%	15,9%
United Kingdom, UK*2 1995/1997 (e45, e46)	5,9%	28%
Maryland*3 USA 1997 (e47)	1,8%	14,2%
Finland 1996 (e48)	4,8%	11%
Statewide, USA 1999 (e49)	4,1%	16,1%

*1 criteria for high- and low-volume hospitals variable
*2 specialized departments versus multi-institutional departments of general surgery
*3 recent results compared with past published data

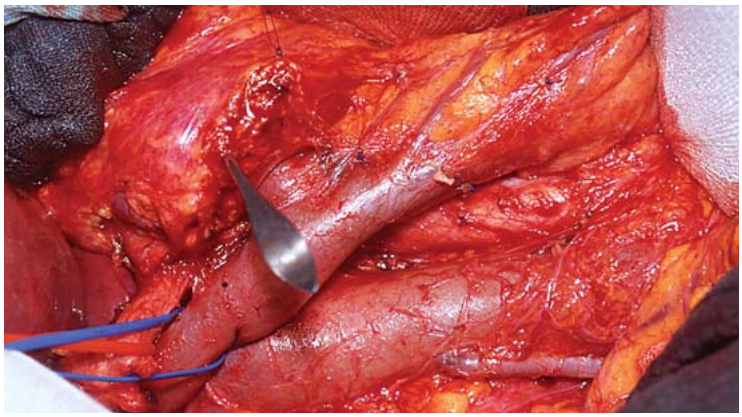


Figure 2: Operative site after standardized resection of a pancreas head cancer. Portal vein and superior mesenteric vein (blue strip) dissected free from tissue; dorsal: intrahepatic vena cava and aorta. Aortocaval space dissected free from lymph nodes (Ulm University Surgical Clinic, Department of General and Visceral Surgery).

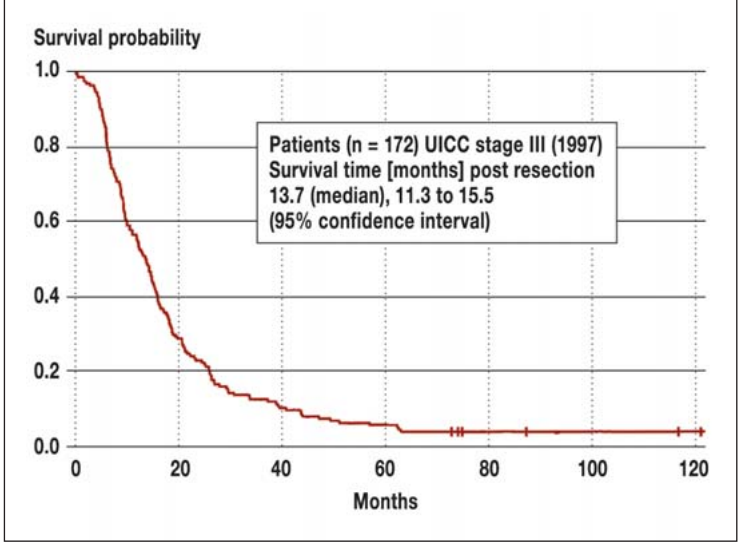
and peritoneum and not by the local relapse. Patients with cancer cells in the resection margin (R1) or a visible tumor left in situ (R2) do not have improved probability of survival after surgical therapy; some data, however, demonstrate that adjuvant palliative chemoradiotherapy can improve the prognosis for the R1/R2 resected patient.

Adjuvant chemotherapy

Prospective randomized studies have shown a significant survival benefit when radical removal of the cancer is supplemented by adjuvant chemotherapy (chemotherapy after R0 resection) or by multimodal adjuvant therapy *(table 8)*. It can be concluded from the data available so far from controlled studies that tumor resection and chemotherapy provide a significant survival benefit in terms of median survival and the 3- and 5-year probability of survival (e61–e64), (20, 25) *(table 8)*. The international ESPAC-1 study initiated in Ulm shows that surgery plus chemotherapy provide a significant median survival of 20.1 months compared to 15 months in the control group (25).

Neoadjuvant radiochemotherapy of pancreatic cancer is not yet recognized and established because of the lack of controlled prospective study data. A detailed assessment of the value of palliative chemotherapy in advanced and metastatic pancreatic cancer was published in Deutsches Ärzteblatt in 2005 (e69).

FIGURE 3



Survival times of 172 patients post resection of a ductal pancreatic cancer in UICC stage III (Ulm University Surgical Clinic [1982-1997])

Prevention

Epidemiological data show that smoking is the cause of about 30% of pancreatic cancers. Tobacco specific carcinogens are methylnitrosamines, nitrosonornicotines, polycyclic aromatic hydrocarbons, and aromatic amines (e66). Case control and cohort studies have shown that cigarette smokers develop pancreatic cancer 3.3 to 9.5 years earlier than nonsmokers. Cigarette smokers have a 70% higher risk of pancreatic malignancy compared to nonsmokers. Smoking filter tip cigarettes does not lower the risk of cancer. Not smoking or permanently stopping smoking is to be classified as a cancer preventive factor (e67).

Patients with alcohol-related chronic pancreatitis, if they are simultaneously long-term smokers, also have an increased risk of cancer of the pancreas and esophagus. The surgical removal of the pancreas head tumor also has a preventive aspect in patients with chronic alcoholic pancreatitis. Since about 10% of all pancreatic cancers develop on the basis of hereditary chronic pancreatitis and a familial genetic predisposition, regular screening examinations (EUS, MDCT) every two to four years are under discussion for the risk groups from age 40 years onwards (e70). No evidence has yet been provided for the effectiveness of screening examinations. However, experience with the use of prophylactic resection in pancreatic diseases with a high cancer risk is so far only available for a small number of patients.

Patients with cystic neoplasms of the pancreas frequently develop pancreatic cancer in the long-term course. With IPMN tumors, malignant transformation to ductal pancreatic cancer is observed in about 60% to 70% of patients (8). In IPMN neoplasia, the carcinoma is predominantly located in the pancreas head. Mucinous cystic neoplasms show malignant transformation in about 20% of cases. Although increasing knowledge of sequential gene mutations in cystic neoplasia of the pancreas does not yet allow reliable risk prediction, experience has shown that surgical removal is indicated for cystic neoplasms measuring above 2 to 3 cm, especially when the diagnosis is known (IPMN,

TABLE 8

Pancreatic cancer, R0 resection and adjuvant chemotherapy; results of controlled (e62, e64) and all randomized multicenter studies published to date

	Patients (number)	Adjuvant therapy	Study patients (number)	Survival*3			
				median (months)	2 years	3 years (percent)	5 years
GITSG 1987 (e61)	43	S+RT+5-FU S	21 22	20 11	42%		19%
YEO 1997 (e62)	120	S+RT+FU S	21 99	19.5 13.5			
EORTC-GITCCG*1 1997 (e63)	228	S+RT+CHT S	108 110	23.5 19.1			
Picozzi *2 2003 (e64)	43	S+RT-FU+Cis+IFNα S+RT+FU	27 16	> 24 18.5	64% 54%	64%	55%
Neoptolemos 2004 (25)	289	S+CT S	75 69	20.1 15		21%	 8%
RTOG 2006 (e65)	442	S+RX/5FU S+Gemza RX/5FU		16.9 20.6		 32%	21%
Oettle 2007 (20)	368	S+Gemza S	147 164	22.1 20.2		34% 20.5%	22.5% 18.5%

S = oncological resection; RT = radiotherapy; EBRT = external beam radiotherapy; CHT = chemotherapy; FU = fluorouracil + folinic acid; Cis = cisplatin; IFNα = interferon α; Gemza = gemcitabine
*1 periampullar tumors included
*2 monoinstitutional, prospective, controlled study
Mean follow-up 31.9 months, 67% of patients still alive
*3 Kaplan-Meier – calculated survival probabilities

MCN, and serous cystic adenoma [SCA]). In many of these diseases, the complete extirpation of cystic neoplasms is a cancer preventive strategy and is now performed without surgical mortality at treatment centers. The complete removal of a cystic tumor (IPMN, MCN) offers patients a cure of the cystic neoplasm and relieves them of the fear of developing pancreatic cancer (e10, e41, e68).

Conflict of interest statement
PD Dr. Rau, Rostock University, participated in the European ESPAC III study. Professor Beger is the founder and Chairman of the German Pancreatic Cancer Foundation (Deutsche Stiftung Pankreaskarzinom), c/o Ulm University Hospital; as the founder of ESPAC he took part in the ESPAC I study. The other authors declare that they have no conflict of interest according to the guidelines of the International Committee of Medical Journal Editors.

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Corresponding author
Prof. em. Dr. med. Dr. h. c. Hans G. Beger
Stiftung Bauchspeicheldrüsenkrebs
c/o Universitätsklinikum Ulm
Steinhövelstr. 9
89075 Ulm, Germany
hans.beger@medizin.uni-ulm.de

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REVIEW ARTICLE

Pancreatic Cancer – Low Survival Rates

Hans G. Beger, Bettina Rau, Frank Gansauge, Gerd Leder, Michael Schwarz, Bertram Poch

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